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Total Synthesis of the Spiroketal Macrolide (+) Milbemycin α_1

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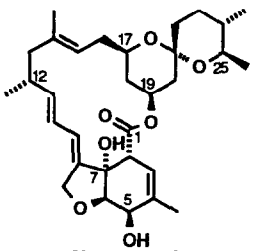
Abstract: The total synthesis of the antiparasitic spiroketal macrolide (+) milbemycin α_1 is reported, following Julia sulfone anion coupling of the sulfone **3** with a northern hemisphere aldehyde **2** and subsequent functional group elaboration.

Owing to their biological activity and structural novelty the milbemycins and avermectins have become popular target molecules for organic synthesis.[1,2] Over the years since their discovery we have delineated a versatile route to these compounds[3] which culminated in the total syntheses of milbemycin β_1[4] and avermectin B_{1a}.[5] Here we report a further application of these methods to the preparation of milbemycin α_1[6,2f] another member of this important series of compounds.

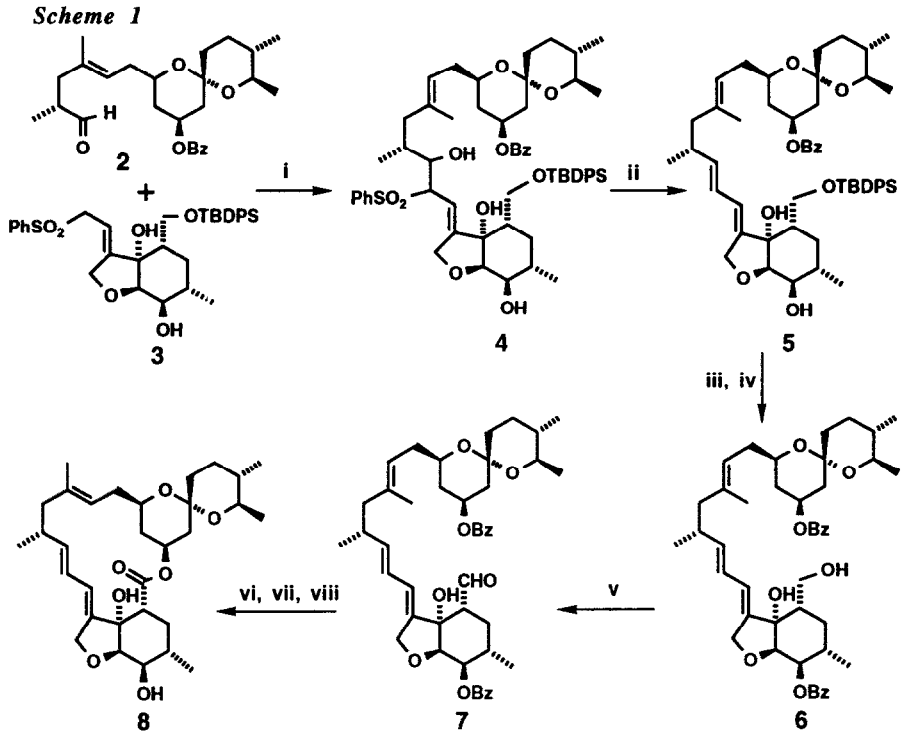


Milbemycin α_1
1

Our previous studies in the area makes available suitable coupling components for this synthesis such as the "northern hemisphere" aldehyde **2**[4] and the allylic sulfone **3**.[5] The sulfone **3** requires no further protection but can be coupled via its trianion using three equivalents of t-butyllithium at -78°C followed by reaction with **2** to give the adduct **4** in 63% yield.[7] Usual Julia reduction[8] of **4** with sodium amalgam gave the *E,E*-diene **5**. This product was benzoylated under standard conditions, then the primary hydroxyl group deprotected by treatment with tetra-n-butylammonium fluoride (TBAF) in THF to give **6** in excellent overall yield. The primary hydroxyl group in **6** was readily oxidised to the aldehyde **7** in 95% yield using oxalyl chloride activated dimethylsulphoxide[9]. While this aldehyde could be isolated it was unstable over time and we found it easier to execute the next steps of the synthesis as rapidly as possible. Oxidation of **7** with sodium chlorite under the Pinnick conditions[10] proceeded satisfactorily to give an intermediate acid as in our previous syntheses which, after removal of the benzoyl groups with sodium methoxide in methanol and Yamaguchi macrolactonisation

with 2,4,6-trichlorobenzoyl chloride[11] and 4-pyrrolidino-pyridine gave **8** in 33% overall yield for the three steps (Scheme 1).

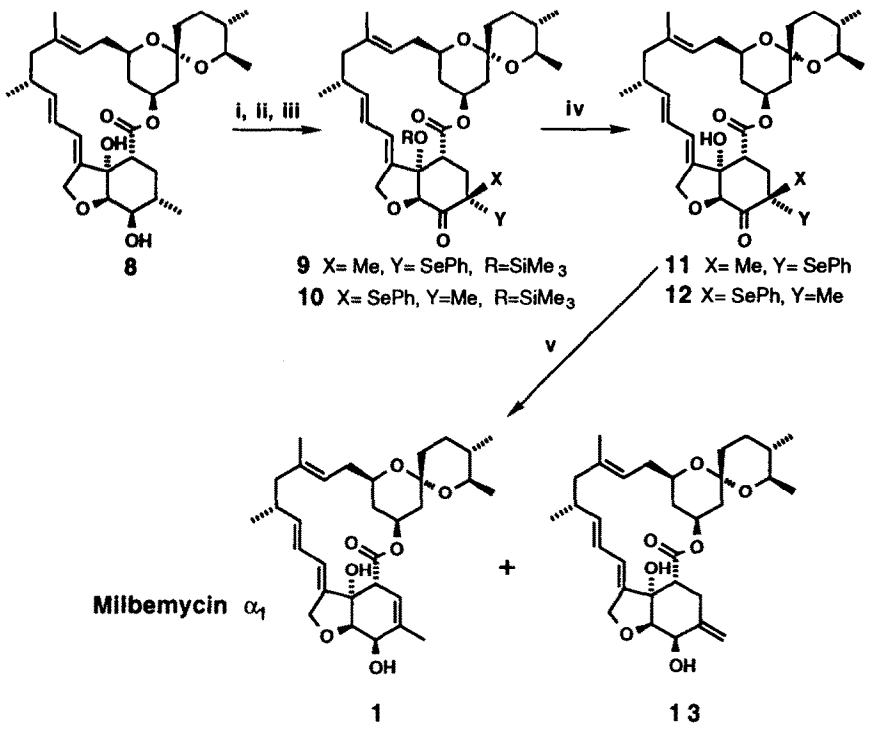
Scheme 1



Reagents and conditions: (i) ^{t}BuLi, THF, -78°C, HMPA, 10 min.; **2**, 1h, (63%); (ii) Na/Hg, Na_2HPO_4, THF/MeOH, -40°C, 45 min., (28%); (iii) BzCl, py/CH_2Cl_2, DMAP, 0°C to RT (95%); (iv) TBAF, THF, 0 °C to RT (88%); (v) DMSO, $(COCl)_2$, CH_2Cl_2, -78°C; Et_3N, -78°C to RT (95%); (vi) $NaClO_2$, $Bu^{t}OH/H_2O$, $Me_2C{=}CHMe$, KH_2PO_4, RT, 1h ; (vii) NaOMe, MeOH; (viii) 2,4,6-trichlorobenzoyl chloride, 4-pyrrolidino-pyridine, Et_3N,CH_2Cl_2, Δ (33% from **7**)

The final stages of the synthesis used a similar approach to that shown to be successful during our avermectin B_{1a} synthesis. Hence oxidation of the hydroxyl function at C-5 with stoichiometric TPAP[12] at room temperature gave the ketone which was selenated at C-4 via the corresponding silyl enol ether using phenylselenenyl chloride to produce the selenides **9** and **10** in good yield and in a 1:1 ratio. These were not separated at this stage but were treated with HF/pyridine to remove the trimethylsilyl group from the C-7 tertiary hydroxyl group to give **11** and **12**. The α-selenide **11** was then converted to the natural product by oxidation with 2(phenylsulphonyl)-3-(*p*-nitrophenyl)oxaziridine to an intermediate selenoxide, subsequent syn-elimination and finally reduction of the resulting enone with $NaBH_4/CeCl_3$. This reaction gave the natural product **1** in 49% together with some (29%) of the exomethylene isomer **13** which was separated by chromatography. The synthetic sample of **1** was identical to an authentic sample of milbemycin α_1 kindly supplied by the Sankyo company.

Scheme 2



Reagents and conditions: (i) TPAP, 4Å molecular sieves, CH_2Cl_2, RT (79%); (ii) $ZnCl_2$, 30 min.; TMSOTf, Et_3N, CH_2Cl_2, 0°C, 6h (85%); (iii) PhSeCl, CH_2Cl_2, -78°C, 2h (**9** : **10**, 1:1; 86%); (iv) HF, py, CH_3CN, RT, 60h (51%); (v) 2-(Phenyl sulphonyl)-3-(*p*-nitrophenyl)oxaziridine, $CDCl_3$, RT, 2h; $NaBH_4$, $CeCl_3$, MeOH, 0°C, 20 min. (49%, **1**; 29%, **13**)

In summary we have shown that a common synthetic strategy developed by our group may be used to synthesize milbemycin α_1, in an analogous fashion to our earlier milbemycin and avermectin syntheses.

Acknowledgements

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References and footnotes

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13) Data for macrolactone **8**: $[\alpha]_D$ =+157 (*c*. 1.0, $CHCl_3$) υ_{max} (film) 3460, 2925, 1701, 1450, 1378, 1270, 1222, 1179, 1056, 997 and 962 cm^{-1} δ_H (500MHz, $CDCl_3$, milbemycin numbering) 5.73-5.67 (2H, m, H-9, H-10), 5.48-5.42 (1H, m, H-19) 5.35-5.30 (1H, dd, J 15.0 and 11.0, H-11), 4.98-4.95 (1H, br. t, J 7.6, H-15), 4.75 (1H, s, C7-OH), 4.65-4.61 (1H, obs. d, J 14.4, 1xH-8α), 4.57-4.54 (1H, obs. d, J 14.4, 1xH-8α), 3.81 (1H, d, J 3.8, H-6), 3.58-3.48 (2H, m, H-5, H-17), 3.29-3.23 (1H, dq, J 9.9 and 6.3, H-25), 2.53 (1H, dd, J 10.0 and 7.5, H-2), 2.43-2.38 (1H, m, H-12), 2.26-2.16 (3H, m), 1.90-1.61 (8H, m), 1.55-1.46 (7H, m inc. C14-Me at 1.51), 1.41-1.37 (1H t, J 11.9), 1.13 (3H, d, J 6.3, Me) 1.08 (3H, d, J 6.4, Me), 0.99 (3H, d, J 6.7, Me), 0.88-0.79 (4H, m inc. Me at 0.82, d, J 6.5); m/z(EI) 530 (0.5%, $[M]^+$), 512 (1.7, $[M-H_2O]^+$), 496 (0.6, $[M-2H_2O]^+$), 281 (2.2, $[C_{14}H_{21}O_5]^+$), 263 (1.6, $[C_{15}H_{19}O_4]^+$), 249 (2.7, $[C_{16}H_{25}O_2]^+$)181 (100, $[C_{11}H_{17}O_2]^+$), 153 (39.9, $[C_{10}H_{19}O]^+$) and 129 (10.5, $[C_7H_{13}O_2]^+$) observed:; $[M]^+$ 530.3243, $C_{31}H_{46}O_7$ requires M^+ 530.3244.

14) Synthetic milbemycin α_1 was found to be identical to the natural product by t.l.c. (3 different solvent systems) and by H.P.L.C. Data for synthetic milbemycin α_1 1: υ_{max} (film) 3462, 2918, 2849, 1732, 1462, 1377, 1261, 1166, 1120, 1056 cm^{-1} ; δ_H (500MHz, $CDCl_3$, milbemycin numbering) 5.80 (1H, dt, 11.3 and 2.4, H-9) 5.73 (1H, dd, 14.3 and 11.3, H-10), 5.44-5.34 (3H, m, H-3, H-11, H-19), 4.99 (1H, t, J 7.8, H-15), 4.71 (1H, dd, J 14.3 and 2.3, 1xH-8α), 4.66 (1H, dd, J 14.3 and 2.3, 1xH-8α), 4.29 (1H, t, J 7.2, H-5), 4.10 (1H, s, C7-OH), 3.96 (1H, d, J 6.2, H-6), 3.52 (1H, m, H-17), 3.29-3.24 (2H, m, H-2, H-25), 2.43 (1H, m, H-12), 2.32 (1H, d, J 8.2, C5-OH), 2.24-2.18 (3H, m, 1xH-13, 2xH-16), 1.99 (1H, ddd, J 12.1, 4.9 and 1.8, H-20_{eq}), 1.89-1.79 (5H, m, 1xH-13, H-18_{eq}, C4-Me at 1.87), 1.67 (1H, m), 1.55-1.47 (6H, m, inc. C14-Me at 1.53), 1.35 (1H, t, J 11.8, H-20_{ax}), 1.26 (1H, m, H-24), 1.15 (3H, d, J 6.3, C25-Me), 1.00 (3H, d, J 6.6, C12-Me), 0.87 (1H, q, J 12.0, H-18_{ax}) and 0.82 (3H, d, J 6.6, C24-Me); m/z (EI) 528 (14.8%, $[M]^+$), 510 (0.6, $[M-H_2O]^+$), 400 (27, $[M-C_6H_8O_3]^+$), 278 (3, $[C_{15}H_{18}O_5]^+$), 261 (2, $[C_{15}H_{17}O_4]^+$), 249 (5, $[C_{16}H_{25}O_2]^+$), 181 (91, $[C_{11}H_{17}O_2]^+$), 153 (72, $[C_{10}H_{19}O]^+$), 129 (10, $[C_7H_{13}O_2]^+$); observed: $[M]^+$ 528.3098, $C_{31}H_{44}O_7$ requires 528.3087.

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